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09/806,645	07/12/2001	Yuri Kolesnikov	830010-2006.	3048

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EXAMINER	
MITCHELL, GREGORY W	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,645	KOLESNIKOV ET AL.	
	Examiner	Art Unit	
	Gregory W Mitchell	1617	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-9,14,15 and 19-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-9,14,15 and 19-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to amendments and remarks filed on October 22, 2004 and the supplemental amendments filed on November 19, 2004. Claims 1, 9, 15, 19, 20, 23, and 27 have been amended. Claims 1, 7-9, 14, 15 and 19-30 are pending and are examined herein.

Applicant's amendments have successfully removed the enablement and obviousness rejections detailed in the previous office action. The 35 U.S.C. 112(1) rejection of claims 27-30 and 35 U.S.C. 103 rejections of claims 1, 7-9, 14, 15 and 19-30 are hereby withdrawn.

The following rejections now apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 recites the limitation "wherein the excipient is ethylene oxide" in line 2. There is insufficient antecedent basis for this limitation in the claim. For examination purposes, Examiner will interpret "ethylene oxide" as a condensation product of ethylene oxide, as recited in claim 27.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, 14, 15, 19-23, 26, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gevirtz et al. (USPN 5635204) in view of both Mayer et al. (USPN 5840731) and Caruso (USPN 5891885).

The instant invention is directed toward a composition comprising ketamine and morphine and a pharmaceutically acceptable topical excipient, wherein the excipient is an aqueous excipient or a gel excipient, and a method of providing analgesia to a mammal comprising topically administering an effective dose of ketamine and morphine.

Gevirtz et al. teaches a method for transdermal induction of anesthesia, analgesia or sedation by simultaneously, transdermally administering fentanyl, an alpha adrenergic agonist and an amnesia inducing drug selected from scopolamine, ketamine, and benzodiazepines (col. 1, line 48-col. 2, line 23; col. 2, line 66-col. 3, line 1). The patches are taught to comprise fentanyl, an alpha adrenergic agonist and an amnesia inducing drug selected from scopolamine, ketamine, and benzodiazepines (col. 2, line 39-col. 3, line 22). Further exemplified are patches comprising carriers such as polyisobutylene (Example 1). Gevertz et al. teaches a transdermal patch comprising 0.45-0.85 mg of the amnesia inducing drug and 20-100 mg of fentanyl (col. 2, line 39-col. 3, line 22). Accordingly, the weight percentage of amnesia inducing drug is 0.4-4.1% of the total weight of amnesia inducing drug plus fentanyl. It is also noted that the

composition of Example 1 teaches a composition comprising 1.5% fentanyl. Gevertz et al. does not teach morphine.

Mayer et al. teaches that the analgesic effectiveness of a combination drug composition comprising at least one analgesic is significantly enhanced by the addition of an NMDA receptor antagonist (Abstract). Mayer et al. teaches compositions comprising a first analgesic, a second component, and an analgesia-enhancing amount of an NMDA receptor antagonist and methods of treatment for alleviating pain by the administration thereof (col. 1, lines 6-27; col. 2, lines 30-col. 3, line 5; col. 4, line 67-col. 5, line 13). Analgesics are taught to be selected from fentanyl, morphine, etc. (col. 3, lines 57-65). NMDA receptor antagonists are taught to be selected from ketamine, etc. (col. 4, lines 33-50). Excipients such as condensation products of ethylene oxide are also taught (col. 5, line 14-col. 6, line 11). Administration is taught to be achieved orally, rectally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, or intracerebroventricularly (col. 4, line 66-col. 5, line 3). It is also noted that the composition of Example 1 comprises about 4% of an opioid analgesic (codeine phosphate).

Caruso teaches pharmaceutical formulations for treating migraines comprising an antimigraine drug and an NMDA receptor blocker. Creams, gels, ointments, lotions, and transdermal patches are taught as interchangeable formulations for topical administration (col. 6, lines 26-32). Compositions for topical administration are taught to be optionally formulated with aqueous or oily bases, thickening, gelling, emulsifying, stabilizing, dispersing, suspending and/or coloring agents (col. 6, lines 26-32).

Excipients such as sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, gum acacia, condensation products of ethylene oxide (wetting agent), etc. are also taught (col. 7, lines 8-27). Administration is taught to be achieved topically, orally, intravenously, intramuscularly, subcutaneously, and rectally (col. 6, lines 22-58).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the fentanyl of Gevirtz et al. with morphine to form a composition comprising morphine, ketamine, and an excipient because (1) both Gevirtz et al. and Mayer et al. are drawn to formulations useful for providing analgesia; (2) both Gevirtz et al. and Mayer et al. teach the combination of an analgesic with an NMDA receptor inhibitor; and (3) Mayer et al. teaches that fentanyl and morphine are interchangeable opioid analgesics, both of which are useful in analgesic/NMDA receptor inhibitor compositions. One of ordinary skill in the art would have been motivated by an expectation of success in providing anesthesia, as taught by Gevirtz et al., and for achieving a significant enhancement of the morphine effect, as taught by Mayer et al.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate the transdermal patches of Gevirtz et al. and the compositions of Mayer et al. as a cream, gel, ointment, or lotion because (1) each of Gevirtz et al., Mayer et al. and Caruso et al. teach compositions comprising a drug and an NMDA receptor inhibitor and methods of administering said composition; (2) Gevirtz et al. and Caruso et al. both teach compositions formulated for topical use; (3) Mayer et al. and Caruso et al. teach compositions comprising similar excipients (e.g. condensation

products of ethylene oxide) and compositions formulated for similar administration (e.g. orally, intravenously, intramuscularly, subcutaneously, rectally, etc.); and (4) Caruso et al. teaches the topical administration of a compositions comprising drug and an NMDA inhibitor as any of a cream, a gel, an ointment, a lotion or a transdermal patch. One of ordinary skill in the art would have been motivated to formulate the compositions of Gevirtz et al. and Mayer et al. as a cream, gel, ointment, or lotion because of an expectation of success in administering the combination for anesthetic/analgesic treatment, as taught by Gevirtz et al. and Mayer et al.

It is noted that the administration of the same composition in the same manner for the same purpose will obviously result in the same result. Accordingly, the topical administration of a topical composition rendered obvious by Gevirtz et al., Mayer et al., and Caruso et al. would obviously deliver morphine to peripheral opiate receptors and not to central opiate receptors.

Claims 7, 8, 24, 25, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gevirtz et al., Mayer et al., and Caruso et al. as applied to claims 1, 9, 14, 15, 19-23, 26, 27 and 30 above, and further in view of Mackles et al. (USPN 5322683).

Gevirtz et al., Mayer et al., and Caruso et al. apply as disclosed above. The references lack the teaching of a local anesthetic.

Mackles et al. teaches that lidocaine is a topical analgesic (col. 3, lines 16-18).

It would have been obvious to one of ordinary skill in the art at the time of the invention to add the lidocaine of Mackles et al. to the composition of the combined reference because (1) the combined references teach a topical analgesic composition; (2) Mayer et al. teaches the use of a second analgesic; and (3) Mackles et al. teaches that lidocaine is a topical analgesic. One of ordinary skill in the art would have been motivated by an expectation of success in providing a second analgesic in further alleviating pain, as taught by Mayer et al.

Response to Arguments/Amendments

Applicant's arguments filed October 22, 2004 and November 19, 2004 have been fully considered but they are not persuasive as they pertain to the 35 U.S.C. 103(a) rejections of claims 1, 7-9, 14, 15 and 19-30.

Applicant argues that "Examiner has picked parts from several references to render a combination that renders Applicants' claims unpatentable, even though the Courts have made it clear that the teaching or suggestion to make the claimed combination, among other things, must both be found in the prior art, and not based on applicant's disclosure." This argument is not persuasive. As Examiner has pointed out in the instant rejection, the combined references are of an analogous art and it would have been obvious to one of ordinary skill in the art at the time of the invention to utilize the teachings of each one to augment the teachings of the others. In particular, each of Gevirtz et al., Mayer et al. and Caruso et al. are drawn to compositions comprising a drug and an NMDA receptor inhibitor and methods of administering said composition.

Applicant further argues, "Gevirtz relates to a transdermal patch and does not teach or suggest topical application of pharmacological agents by an aqueous solution, gel, lotion, ointment, cream or spray." This argument is not persuasive because Examiner does not rely on Gevirtz et al. for the teaching of aqueous solution, gel, lotion, ointment, cream or spray, but relies on Caruso et al., as described above. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); MPEP 2145.

Applicant's arguments regarding that the Needham paste and the Nelson matrix are not topical pharmaceutical compositions are moot in view of the instant rejections. Applicant's arguments that Kaneko relates to an epidural injection, not a topical application is rendered moot by the instant rejections.

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8:30 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

gwm

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER